

REMARKS

The present claims are drawn to methods for treating pain with spingosine. Applicant has surprisingly discovered that spingosine can be safely used to treat pain. As the specification explains at page 2, certain A1 adenosine receptor agonists have been found have analgesic activity and certain A2 adenosine receptor agonists have been found anti-inflammatory activity. However, as also explained at page 2 of the specification, A1 receptor agonists are known cause bradycardia and A2 adenine receptor agonists are known cause vasodilatation leading to hypotension and tachycardia. For these reasons, adenosine receptor agonists were commonly considered to have limited usefulness in treatment of pain. Despite these teachings, which would discourage one from investigating adenosine receptor agonists, particularly spingosine, which was shown by Ueeda et al. have dangerous side effects, for treatment of pain, Applicants discovered that spingosine can be used to safely and effectively treatment pain in human patients.

This response addresses the rejections made in the Office Action mailed 15 May 2009. Applicant previously filed an RCE accompanied by an amendment that amended claim 11.

I. Amendment of the claims

Claim 11 was previously amended to specify that the subject is a human subject.
No new matter was added by this amendment.

II. Anticipation Rejection under 35 U.S.C. § 102(b)

Claims 11-14, 16, 17, 19-31 and 47-52 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bartlett et al. (*J. Med. Chem.* 24:947-954, 1981) The Examiner stated that Bartlett et al. discloses administration of spingosine to treat carrageenan-induced inflammation. The Examiner argued that this treatment must have inherently resulted in the suppression of pain.

Bartlett et al. does not describe administration of spingosine to a human subject. Thus, irrespective of whether administration of spingosine to rats at a level reduced inflammation resulted in inherent treatment pain, Bartlett et al. cannot anticipate any of the pending claims, all

of which depend directly or indirectly from claim 11, which now recites treatment of a human subject.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

III. Obviousness Rejection under 35 U.S.C. § 103(a)

Bartlett et al. and Herrick-Davis et al.

Claims 11-14, 16, 17, 19-31 and 47-52 were rejected under 35 U.S.C. § 103(a) as being obvious in view Bartlett et al. and Herrick-Davis et al. (*European Journal of Pharmacology*, 162:365-369, 1989).

The Examiner stated that Herrick-Davis et al. discloses that a variety of adenosine analogues that are known in the art to be adenosine receptor agonists and have been found to be analgesic agents with efficacy comparable to morphine. The Examiner argued that one of the compounds tested, 2-chloroadenosine (CADO), is a close structural relative to spongosome. The Examiner argued that it would have been obvious "to conclude that compounds very closely analogous to CADO disclosed to be a potent analgesic by Herrick-Davis et al. to be consistent with an analgesic effect of spongosome as disclosed by Bartlett et al. in the treatment of an inflammatory response." The Examiner argued that one of ordinary skill in the art would have been motivated to combine these references because both references are directed to disclosures of the analgesic effects observed following the administration of 2-substituted analogues of adenosine, including spongosome.

Applicant respectfully traverses this rejection. However, before discussing the rejection in detail, Applicant respectfully points out that, contrary to the implication in the statement by the Examiner quoted above, Bartlett et al. does not disclose any analgesic effect of spongosome – only an anti-inflammatory effect is disclosed.

Structurally similar compounds do not necessarily exhibit similar properties

It is well established that structural similarity does not give rise to obviousness in the absence of similar properties ("it is not structural similarity alone that gives rise to obviousness, but the concomitant assumption that the structurally similar compounds will have like

properties.” *Ex Parte Chwang* 231 USPQ 751, 752 (Bd. Pat. App. & Int’f 1986). In the present case, the art teaches that CADO has properties that differ from structurally related compounds.

CADO is shown in Ueeda et al. (*Life Sciences* 49:1351-1358) to have substantially different binding constants at A₁A and A₂A receptors as compared with 2-ethoxyadenosine. In particular, the inhibition constant K_i of CADO (#3) at A₁AR differs from that for 2-ethoxyadenosine (#13) by a factor of 132 in rat and 170 in guinea pig. Furthermore, according to Ueeda et al., 2-ethoxyadenosine (#13) is selective for the A₂AR receptor, whereas compounds including CADO (#3) are unselective (Ueeda et al., page 1354, lines 3-4). Consequently, because the Ueeda et al. reference teaches that there are substantial differences between 2-ethoxyadenosine and CADO, one of ordinary skill in the art would not expect another 2-alkoxyadenosine such as spongosine (2-methoxyadenosine) to have similar properties to CADO. Contrary to the Examiner’s allegation, one of ordinary skill in the art would not view CADO as closely analogous to spongosine. Thus, disclosure of CADO as an analgesic in Herrick-Davis et al. does not support an obviousness rejection of the claimed method of treating pain which comprises administering spongosine (2-methoxyadenosine) to a human subject in need of such treatment.

Even assuming spongosine exhibited properties similar to CADO, one would avoid its use in treatment of humans

Moreover, even if one were to assume that CADO and spongosine have similar properties, one would not be motivated to use spongosine for treatment of pain in humans.

This is because Ueeda et al. teach that at a dose at which spongosine reduced inflammation by 25%, blood pressure dropped by a striking 41% and heart rate by 25%. Clearly, such side effects would not be even remotely tolerable in the treatment of pain in humans. Thus, one skilled in the art would not consider using spongosine for treatment of pain even if one assumed that spongosine had analgesic properties similar to those of CADO.

Moreover, Bartlett et al. suggest that the harmful side effects observed with adenosine analogues consistently accompany anti-inflammatory activity: “The muscle relaxant, hypothermic, and hypotensive effects of 1-methylisoguanosine, as well as a number of the analogue, were accompanied by a decrease in heart rate. **None of the analogues investigated**

had any selectively of action whereby the bradycardia [reduced heart rate] could be removed or reduced while maintaining the other pharmacological effects.” (Bartlett et al. at 950; emphasis added). Given the detrimental side effects observed by Ueeda et al. and given that the side effects are observed with several adenosine analogues that have anti-inflammatory activity, one of ordinary skill in the art would not be motivated to use spongosome to treat pain in humans. Indeed, one skilled in the art would endeavor to avoid the use of spongosome.

For the forgoing reasons, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

Applicant surprisingly found that spongosome can be used to safely treat pain and can do so at a dose that gives rise to a plasma concentration below the K_d for the adenosine receptor

As the specification explains at page 2, certain A1 adenosine receptor agonists have been found have analgesic activity and certain A2 adenosine receptor agonists have anti-inflammatory activity. However, as also explained at page 2 of the specification, A1 receptor agonists cause bradycardia and A2 adenine receptor agonists cause vasodilatation leading to hypotension and tachycardia. For these reasons, adenosine receptor agonists were commonly considered to have limited usefulness in treatment of pain.

Despite these teachings, which would discourage one from investigating adenosine receptor agonists, particularly spongosome, which was shown by Bartlett et al. have dangerous side effects, for treatment of pain, Applicants discovered that spongosome can be used to safely and effectively treatment pain in human patients. In addition, Applicants surprisingly found that spongosome can be used to treat pain even when administered at a very low dose. As the specification explains at page 9, spongosome was “effective in inhibiting pain perception in mammals suffering from neuropathic and inflammatory pain even when administered at doses expected to give concentrations well below those known to activate adenosine receptors.”

In view of the forgoing, even if the presently claimed invention were *prima facie* obvious in view of the cited references, which it is not, Applicant's unexpected results are more than sufficient to overcome the *prima facie* case. For this reason, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

Fukunaga and Sollevi Patents

In rejecting claims 11-14, 16, 17, 19-31 and 47-52 as obvious in view Bartlett et al. and Herrick-Davis et al., the Examiner stated that "Herrick-Davis et al. has additional support in the form of the previously cited Fukunaga patent reference, the newly cited Fukunaga patent references, and the newly cited Sollevi patent references, all of which disclose that adenosine has been established to have analgesic activity". The Examiner went on to state that "the question of a correlation between analgesic activity and 2-substitution in adenosine and adenosine analogues suggests that small 2-substituents may not have much effect on the analgesic activity of adenosine, and therefore that 2-substituted analogues of adenosine can be expected to have analgesic activity similar to that of adenosine itself."

Applicant respectfully requests that the Examiner clarify whether the Examiner is rejecting any of the pending claims as obvious in view of any of the Fukunaga or Sollevi patents noted on the PTO-892 form accompanying the Office Action. If so, Applicant respectfully requests that the Examiner state the claims being rejected and combination of references that forms the basis of the rejection so that Applicant can respond to the rejection.

While it unclear whether the Examiner is rejecting any of the pending claims based on Fukunaga and Sollevi, it does appear the Examiner believes that these references suggest that substitution at the 2 position of the adenine ring of adenosine does not impact analgesic properties. Of course, the same reasoning would suggest that substitution at the 2 position of the adenine ring does not impact other properties. However, according to Fukunaga '209, adenosine has a half-life in the human body of just a few seconds. In contrast, the half-life of spongosine in the human body is far, far longer – about 1 hour and 40 minutes (see Declaration of Peter Richardson, Ph.D., enclosed herewith). Moreover, as discussed above in regard to Uedda, substitution at the 2 position of the adenine ring can dramatically impact receptor binding. Thus, 2-ethoxy adenosine is selective for the A2 receptor over the A1 receptor whereas CADO is non-selective. Applicant reserves the right to comment further on the Fukunaga and Sollevi references should the Examiner actually base a rejection on one or more these references.

IV. Enablement Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 11-14, 16, 17, 19-31 and 47-52 for lack of enablement. The Examiner stated that while the specification is enabling "for the treatment of inflammation, hypertension, and pain by the administration of spongiosine, or a combination of spongiosine and the amino acid gabapentin, does not reasonably provide enablement for the treatment of any of the noted conditions with other mixtures of spongiosine and another analgesic acid as disclosed in claims 27 and 28.

Except for claims 27 and 28, the pending claims do not recite the administration of an agent other than spongiosine. Accordingly, Applicant respectfully requests that, the Examiner withdraw this rejection as applied to claims 11-14, 16, 17, 19-26, 29-31 and 47-52.

Regarding claims 27 (which recites an analgesic agent in combination to spongiosine) and 28 (which recites specific classes of analgesic agents in combination with spongiosine), it is Applicant's position that those skilled in the art are aware of many, many analgesic agents and would know how to treat patients with these analgesic agents. In view of this, it is Applicant's position that claims 27 and 28 are enabled, and Applicant requests that the rejection of claims 27 and 28 under 35 U.S.C. §112, first paragraph for lack of enablement be withdrawn.

V. Obviousness-type double patenting rejections

The Examiner provisionally rejected claims 11-14, 16, 17, 19-31 and 47-52 under the judicially created doctrine of obviousness type double patenting over claims 16-33 of co-pending Application Ser. No. 10/547,455, filed March 5, 2004, and claims 13-24 of co-pending Application Ser. No. 10/547,454, filed March 5, 2004.

The allegedly conflicting claims of Application Ser. Nos. 10/547,455 and 10/547,454, have not been patented. Applicant will address any obviousness type patenting rejections upon notification that there are claims which are otherwise allowable.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal

Applicant : Peter Richardson
Serial No. : 10/537,564
Filed : August 28, 2006
Page : 12 of 12

Attorney's Docket No.: 13425-0170US1 / BV-1083 US

of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at 617.542.5070.

No fee is believed to be due. If, however, there are any charges or credits, please apply them to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 24 November 2009

/Anita L. Meiklejohn/
Anita L. Meiklejohn, Ph.D.

Customer No. 26161
Fish & Richardson P.C.
Telephone: (650) 839-5070
Facsimile: (650) 839-5071